Acetaminophen Overdose and Liver Injury — Background and Options for Reducing Injury

What Is the Problem?

Acetaminophen is one of the most commonly used drugs in the United States for treating pain and fever 1—in 2005, consumers purchased more than 28 billion doses of products containing acetaminophen, and the hydrocodone—acetaminophen combination product has been the most frequently prescribed drug since 1997 (See Box 1). However, exceeding the maximum recommended dose of acetaminophen (4 grams per day) can cause serious liver injury—even death. Despite a number of efforts since the early 1990s to reduce the incidence of acetaminophen-related liver injury, the extent of liver failure cases reported in the medical literature indicates that liver injury from acetaminophen overdose remains a serious public health problem. This problem will be discussed at a joint meeting of the Drug Safety and Risk Management Advisory Committee, the Nonprescription Drugs Advisory Committee, and the Anesthetic and Life Support Drugs Advisory Committee on June 29 and 30, 2009.

What Is Acetaminophen and What Is It Used For?

Acetaminophen is the generic name of a drug found in many common brand-name over-the-counter (OTC) products (e.g., Tylenol, Excedrin) and prescription (Rx) products (e.g., Vicodin and Percocet). Acetaminophen is an important drug, and its effectiveness in relieving pain and fever is widely known. Unlike other drugs commonly used to reduce pain and fever (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin, ibuprofen, and naproxen), at recommended doses acetaminophen does not cause stomach discomfort or bleeding. To date, the agency has considered acetaminophen safe when used according to the directions on its OTC and Rx labeling. Taking more than the recommended dose of 4 grams a day, however, can cause liver damage, ranging from abnormalities in blood tests used to assess liver function to acute liver failure (ALF), and even death. Many cases of acetaminophen overdose are caused by consumers inadvertently taking more than the recommended dose.

Box 1: Acetaminophen Use

In 2005, U.S. consumers purchased more than 28 billion doses of products containing acetaminophen of which:

- Single ingredient OTC products (e.g., Tylenol) represented 8 billion doses.
- Combination OTC products (e.g., NyQuil and Theraflu), represented more than 9.7 billion doses.
- Acetaminophen-containing Rx narcotics represented 11 billion doses.
 - Between 2001 and 2005, use of these combination Rx products increased 38%.
 - There were more than 182 million prescriptions for combination Rx products in 2005.
 - The most frequently used acetaminophen-containing prescription product is the hydrocodone/acetaminophen combination. It has been the most frequently dispensed Rx drug since 1997.

¹ Kaufman DW, Kelly JP, Rosenberg L, Anderson TE, Mitchell AA. Recent patterns of medication use in the ambulatory adult population of the United States: the Slone survey. JAMA, 2002 Jan 16; 287(3) 337-44. See also http://www.bu.edu/slone/SloneSurvey/SloneSurvey/SloneSurvey.htm.

² IMS Health, IMS National Sales Perspectives™, Year 2005, Extracted 9/06.

³ SDI, Vector One®: National. Year 2005, Extracted 11/06.

⁴ In some people, particularly those who consume much alcohol or have underlying liver disease, even 4 grams per day may cause liver injury.

⁵ See http://www.fda.gov/OHRMS/DOCKETS/98fr/E9-9380.pdf

How Does Liver Injury Occur?

The mechanism of liver injury is related to the fact that small amounts of acetaminophen are converted to a toxic metabolite. The toxic metabolite binds with liver proteins to cause cellular injury. The amount of toxic metabolite produced and the ability of the liver to remove this metabolite before it binds to liver protein influence the extent of liver injury.

How Common is Liver Injury Due to Acetaminophen Overdose?

A number of studies have tried to answer this question. However, many questions remain about the full scope of the problem. Nonetheless, what is known about the extent of liver failure cases reported in the medical literature clearly indicates a reason for concern. (See Box 2).

Box 2: Liver Injury, Population Overall

- From 1998 to 2003, acetaminophen was the leading cause of acute liver failure in the United States, with 48% of acetaminophen-related cases (131 of 275) associated with accidental overdose.*
- A 2007 CDC population-based report estimates that, nationally, there are 1600 cases of ALF each year (all causes). Acetaminophen-related ALF was the most common etiology.**
- Summarizing data from five different surveillance systems, there were an estimated 56,000 emergency room visits, 26,000 hospitalizations, and 458 deaths related to acetaminophen-associated overdoses per year during the 1990-1998 period. ***

In a study that combined data from 22 specialty medical centers in the United States, acetaminophen-related liver injury was the leading cause of ALF for the years 1998 through 2003. This study also found that a high percentage of cases of acetaminophen liver injury were related to unintentional overdose, in which the patient mistakenly took too much acetaminophen. This finding was confirmed in a later study (2007). Many other cases of acute liver injury are caused by intentional overdoses of acetaminophen (e.g., associated with self-harm).

Across various studies, consumers were found to have taken more than the recommended dose when using an OTC product, an Rx product, or both. The Toxic Exposure Surveillance System (TESS), which captures data from calls to 61 poison control centers, provides additional data on acetaminophen overdose and liver injury. In 2005, TESS showed that calls about poisoning cases that resulted in major

^{*} Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Lee WM et al. Acute Liver Failure Study Group (ALFSG). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology, 2005 Dec; 42(6):1364-72.

^{**} Bower WA, Johns M, Margolis, HS, Williams IT, Bell B. Population-based surveillance for acute liver failure. Am J Gastroenterol, 2007;102:2459-63.

^{***} Nourjah et al. Estimates of Acetaminophen (Paracetomil)-associated overdoses in the United States, Pharmacoepidemiol Drug Safety 2006 Jun, 15(6).

⁶ Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Lee WM et al. Acute Liver Failure Study Group (ALFSG). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*, 2005 Dec; 42(6):1364-72.

⁷ Bower WA, Johns M, Margolis, HS, Williams IT, Bell B. Population-based surveillance for acute liver failure. *Am J Gastroenterol*, 2007;102:2459-63.

injury numbered 1,187 for OTC single-ingredient products, 41 for OTC combination products, and 1,470 for Rx combinations.⁸

Why Do Acetaminophen Overdoses Occur?

There are few available data describing consumer behavior with acetaminophen products or consumer understanding of acetaminophen toxicity. However, a number of factors that may contribute to this public health problem are outlined here.

- In some individuals, taking just a small amount more than the recommended total daily dose of acetaminophen (4 grams per day) may lead to liver injury. Acetaminophen has a narrow safety margin. This means that there is little difference between the maximum recommended daily dose and a potentially harmful dose. There is scientific agreement that taking a large amount of acetaminophen over a short period of time causes liver injury, but there are varying views on the specific threshold dose for toxicity.
- Some individuals may be especially prone to liver injury from acetaminophen. The maximum amount of acetaminophen that can be safely ingested may not be the same for all people. Available data suggest that some individuals, especially those who use alcohol or have liver disease, may have a greater susceptibility to the effects of the toxic metabolite because they produce more of the metabolite or because they are unable to clear it from the body as easily. Individuals with increased susceptibility may experience toxic effects at lower acetaminophen doses than others—rare cases of acute liver injury have been linked to amounts lower than 2.5 grams per day. ¹⁰ More research is needed to understand whether ethnicity, genetics, nutrition, or other factors might play a role in making some individuals more prone to liver injury.
- It can be difficult to recognize the onset of liver injury. The onset of symptoms associated with acetaminophen liver injury can take several days, even in severe cases. In addition, symptoms may be non-specific and mimic flu symptoms, resulting in the individual continuing to use acetaminophen.¹¹
- There are many different types of OTC and Rx acetaminophen products and a range of doses for a variety of different indications. Acetaminophen can be found in many widely used OTC single ingredient products (e.g., to treat headaches) and in multiple ingredient (combination) products (e.g., in products to treat symptoms of the common cold). Acetaminophen is also a component in a number of Rx drug products in combination with narcotic pain medicines. Consumers may attempt to treat different conditions or symptoms at the same time with more than one product containing acetaminophen. They may not realize that acetaminophen is in each of those products and that they are at risk of acetaminophen overdose.

⁸ 2005 Annual Report of the American Association of Poison Control Centers' National Poisoning and Exposure Database. Lai MW, Klein-Schwartz W, Rodger GC, Abrams JY, Haber DA, Bronstein AC, Wruk KM. Clinical Toxicology, 44:803–932, 2006

⁹ Data from both FDA's Adverse Event Reporting System (AERS) and the Acute Liver Failure Study Group (ALFSG) show that the median daily dose of acetaminophen related to liver injury was 5 to 7.5 grams/day, very near the current maximum daily dose of 4 grams/day.

¹⁰ Lee W. Drug-induced hepatotoxicity, *New England Journal of Medicine*, July 31, 2003; 349:474-485.

¹¹ Symptoms include nausea, vomiting, diaphoresis, and general malaise. Clinical and laboratory evidence of liver injury may not be apparent until 48 to 72 hours post-ingestion. N-acetylcysteine can prevent liver injury if given within 12 hours of a single ingestion; however, unintentional overdosing is usually only recognized after symptoms have developed.

- Many consumers do not know that acetaminophen overdoses can cause serious liver injury.¹² Consumers may consider acetaminophen a familiar product that has been marketed for decades and therefore assume that the medicine is completely safe. This perception may be reinforced by the fact that the drug is widely available OTC in very large quantities (e.g., 500 tablets per bottle). Furthermore, advertisements of OTC products are not required to provide warning information.
- It can be difficult to identify acetaminophen as an ingredient in Rx products. Rx products that contain acetaminophen (usually with codeine, oxycodone, or hydrocodone) are often labeled as containing *APAP*, rather than *acetaminophen*, on pharmacy-dispensed containers. ¹³ Without clear labeling, people may take more than one product containing acetaminophen (e.g., an Rx product and an OTC product) without realizing they may be taking a harmful dose of acetaminophen.
- Liquid products for children are available in different concentrations. Liquid acetaminophen formulations intended for use in infants are typically more concentrated (i.e., stronger) than for older children to enable dosing using less liquid. It is possible to mistakenly overdose an older child by giving him or her a product intended for an infant.

What Has FDA Done to Address the Problem?

In the late 1990s, research began to show that acetaminophen was a major cause of ALF in the United States, with up to half of the cases due to unintentional overdose. Responding to these concerns, FDA began taking steps to reduce the incidence of liver injury related to acetaminophen.

- In 1998, FDA finalized a regulation requiring alcohol warnings be added to OTC labeling. The
 regulation required all OTC acetaminophen products to include an alcohol warning in their labeling.
 The warning advised consumers who ingest 3 or more alcoholic drinks every day to ask their doctor
 whether they should take acetaminophen or other pain relievers/fever reducers.
- In 2002, FDA held a public advisory committee meeting.

 14 The advisory committee meeting focused on unintentional liver injury related to the use of OTC acetaminophen. The advisory committee recommended a specific liver toxicity warning and distinctive labeling on OTC packages so that acetaminophen could be more easily identified as an ingredient. FDA and manufacturers were also advised to educate consumers and health professionals about the risk of liver injury from acetaminophen.
- In early 2004, FDA launched a public education campaign. The goal of this ongoing public
 education campaign is to help consumers understand how to use both NSAIDs and acetaminophen
 medicines more safely. FDA continues to expand efforts to improve public education about
 acetaminophen overdosing and liver injury and has recently updated the acetaminophen information
 on FDA's Web site.
- In 2004, FDA requested assistance from state boards of pharmacy in reducing acetaminophen-related liver injury. FDA sent letters to every U.S. state board of pharmacy asking them to consider adding new requirements for pharmacy-generated Rx labeling of products containing acetaminophen. The prescription labeling would (1) use the term acetaminophen, not APAP, (2) instruct patients to avoid concurrent use of other acetaminophen containing drugs, (3) instruct patients not to exceed the maximum daily recommended acetaminophen dose, and (4)

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¹² Stumpf JL, Skyles AJ, Alaniz C, Erickson SR. Knowledge of appropriate acetaminophen doses and potential toxicities in an adult clinic population. *J Am Pharm Assoc* (2003). 2007 Jan-Feb; 47(1): 35-41.

¹³ APAP is an acronym based on the chemical name of acetaminophen, N-acetyl-para-aminophenol.

¹⁴ See http://www.fda.gov/ohrms/dockets/ac/cder02.htm#NonprescriptionDrugs.

instruct patients to avoid drinking alcohol during prescription use. ¹⁵ FDA was informed by the National Association of Boards of Pharmacy that, as of February 2008, no states had implemented regulations related to this request.

- In 2007, the Director of FDA's Center for Drug Evaluation and Research (CDER) convened a multidisciplinary working group to review safety issues related to acetaminophen. He asked the working group to evaluate issues associated with acetaminophen-related liver injury and consider additional steps FDA could take to decrease the number of cases of acetaminophen-related liver injury. As part of its deliberations, the working group considered detailed reviews from CDER's Office of Nonprescription Products, Office of Surveillance and Epidemiology, and Division of Anesthesia and Analgesic and Rheumatology Drug Products. The working group recommended implementation of additional public health interventions. Given the complex nature of the underlying problem of acetaminophen liver toxicity, the Center Director and the working group agreed that any possible options beyond the labeling rules proposed in 2006 (which were being finalized) should be presented for public discussion prior to FDA's taking further action.
- In April 2009, FDA issued a final regulation that strengthens labeling for OTC products containing acetaminophen. ¹⁶ Box 3 lists some of the final labeling requirements for OTC products containing acetaminophen, which include more specific warnings about liver injury, the role of alcohol in increasing the risk of liver injury, and the importance of avoiding the use of more than one product that contains acetaminophen.

Box 3: Labeling Requirements for OTC Products Containing Acetaminophen, April 2009

- Alcohol warning is part of liver warning (instead of separate alcohol warning previously required).
- Warning includes information on potential for severe liver damage associated with exceeding the maximum daily dose or taking three or more alcoholic drinks a day while taking acetaminophen.
- The liver warning is required on immediate container labels in addition to the carton or outer container.
- Ingredient name (i.e., a cetaminophen) is highlighted or in bold type and in a prominent print size on the package's principal display panel (PDP).
- Statement "See new warnings information" is highlighted or in bold type and in a prominent print size on the PDP.
- Label contains concomitant use warning to avoid use of other acetaminophen products and direction to ask a doctor before taking acetaminophen in the presence of liver disease or if using warfarin.
- FDA is expanding its existing educational programs. We are undertaking a much larger and more comprehensive educational campaign than has occurred in the past, intended to reach both the general public and healthcare professionals to raise awareness about acetaminophen and liver injury and to encourage safe use practices. Specific messages include:
 - Take no more than the recommended dose of acetaminophen

¹⁵ Letter from Steven Galson to State Boards of Pharmacy, *Acetaminophen Hepatotoxicity and Nosteroidal Anti-Inflammatory Drug (NSAID)-Related Gastrointestinal and Renal Toxicity* (January 22, 2004), available on FDA's Web site at http://www.fda.gov/cder/drug/analgesics/letter.htm.

¹⁶ Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Final Monograph (Docket No. FDA-1977-N-0013), 74 FR 19385 (April 29, 2009).

- Do not mix acetaminophen-containing products
- Talk to your doctor about acetaminophen if you consume alcohol or have liver disease

What Options to Address This Problem Have Been Identified for Discussion at the Advisory Committee Meeting?

CDER staff have reviewed the interventions recommended by the acetaminophen working group to reduce the incidence of liver injury and have developed options for discussion at the Advisory Committee meeting. The options are summarized briefly here and discussed in more detail in the section, Options – Key Considerations. The agency is seeking advice from the Advisory Committee on what options would be ideal to control the overdoses associated with acetaminophen products. FDA will then evaluate the recommendations and assess whether there are regulatory pathways available to the agency to accomplish its goals and, if so, the advantages and disadvantages of each pathway. Such an evaluation, and implementation of selected options, will take some time.

Summary of Options

Option 1: Reduce current doses (e.g., current maximum adult daily dose, single adult dose, and tablet strength). Alternatively, restrict current maximum adult daily dose, single adult dose, and tablet strength to Rx only.

Acetaminophen has a narrow safety margin. This means there is little difference between the maximum daily dose and a potentially harmful dose. This option involves reducing the amount of acetaminophen recommended as a daily dose for OTC, and perhaps also Rx products, to decrease the likelihood that patients will unintentionally exceed safe doses. Alternatively, any amount of acetaminophen greater than 325 mg per tablet (650 mg recommended dose) could be restricted to Rx only.

Option 2: Establish package size limits for OTC acetaminophen products

Today, consumers can purchase acetaminophen OTC from a variety of pharmacies and drug stores in a variety of package sizes, containing up to hundreds of doses. Limiting the number of acetaminophen doses (e.g., tablets, capsules, liquids) in a package and potentially introducing sales restrictions, might alert consumers to the need to use acetaminophen safely and may be particularly useful in reducing the incidence of intentional poisonings associated with acetaminophen.

Option 3: Require unit-of-use packaging for prescription products

Many products come to pharmacies in bulk, enabling the pharmacist to repackage to suit individual patient needs. *Unit-of-use packaging* means the product comes to the pharmacy packaged ready for sale without having to be repackaged. This proposal would enable FDA to standardize the information laid out on the prescription label, warnings, and description of active ingredients (i.e., acetaminophen instead of APAP). Armed with appropriate risk information, patients would be able to reduce the risk of unintentional overdose.

Option 4: Expand product warning information on Rx products

FDA recently issued new regulations for labeling OTC products containing acetaminophen. As a result, this option focuses primarily on improving Rx labeling. If all acetaminophen-containing Rx products were required to consistently and prominently identify *acetaminophen* as an ingredient (and not use different terms, such as *APAP*), it might be easier for consumers to identify this ingredient.

Option 5: Eliminate combination OTC and/or Rx products that contain acetaminophen

Rx products and many OTC products contain acetaminophen along with other active ingredients. Consumers are not always aware when acetaminophen is present in these combination products and take them with other acetaminophen-containing products. Eliminating combination products that contain acetaminophen may reduce the risk of duplicate dosing.

Option 6: Limit dosing formulations for OTC liquid products; require dosing device

Acetaminophen is available in liquid form primarily for children, but also for adults. Today, liquid acetaminophen comes in two strengths, a suspension for older children and a more concentrated liquid, referred to as *infant drops*. Sometimes the availability of multiple strengths causes confusion when treating children. This option proposes that all liquid products be made in the same concentration. In addition, manufacturers would be required to include in each package a measuring device (spoon or container), properly calibrated and clearly marked for product dosing, making it easier for caregivers to give the appropriate dose.

Options — Key Considerations

In weighing the various options, a variety of different factors must be considered to determine how useful a particular option would be in reducing the incidence of acetaminophen-related liver injury and whether it should be adopted. These factors include:

- The effect an option would have on prescribers, consumers, and caregivers, including benefits, costs, and potentially unintended consequences
- How long it would take to implement the option (if engaging in rulemaking is required, the process sometimes takes years)¹⁷
- The effect an option would have on companies producing or pharmacies dispensing products containing acetaminophen

An analysis of each option regarding these factors is presented in the following sections. In some cases, issues—about which little information is available—were raised, and these are noted. In other cases, the option to be implemented may require changing existing regulations, going through a process called *rulemaking*; this is a time-consuming process with an unpredictable outcome (see Box 4).

Box 4: OTC Monograph Changes are Made Through Rulemaking

Rulemaking is a complex activity that requires:

- Development and publication of a proposed rule (often requiring a year or more).
- An extensive economic analysis to assess whether the economic burden outweighs the benefits.
- Review of comments to the proposed rule, finalization of the regulation, and publication of the final regulation (often requiring a year or more).

As noted above, the agency is seeking advice from the Advisory Committee on what options would be ideal to control the overdoses associated with acetaminophen products. FDA will then evaluate the recommendations and assess whether regulatory pathways are available to the agency to accomplish its goals and if so, the advantages and disadvantages of each pathway. Such an evaluation, and implementation of selected options, will take some time.

Option 1a: Reduce current dosage strengths (including the recommended maximum adult daily dose, the single adult dose and dosage strengths in OTC and Rx products)

Current Situation

Acetaminophen has a narrow safety margin in that there is only a small difference between the maximum daily dose and a potentially harmful dose. OTC acetaminophen products are formulated to

¹⁷ Products available OTC are sometimes regulated under new drug applications, but nearly all acetaminophen-containing OTC products are regulated under the OTC Drug Review. This system established monographs for certain categories of OTC products and sets limits on ingredients, formulations, labeling, and dosage. Changes to how OTC acetaminophen is labeled would therefore require that the monograph be changed. Such changes require all of the standard processes of any FDA rulemaking.

contain either 325 mg or 500 mg per single tablet or capsule. Most products on the market today contain the higher dosage, which is labeled to provide a recommended single adult dose of 1000 mg and a maximum adult daily dose of 4 g (4000 mg). OTC liquid products for adults are made to deliver doses in the same increment (e.g., 500 mg per 5 mL). The amount of acetaminophen in Rx product tablets ranges from 150 mg to 750 mg per tablet.

Option

Reduce current dosage strengths: the recommended maximum single dose to 650 mg and the recommended maximum daily adult dose to 2600 mg. Tablets, capsules, and liquids would need to be reformulated to maximum increments of 325 mg. This option would apply to both single-ingredient and combination products. It could be applied only to OTC products, or could additionally be applied to Rx combination products.

Intended Effect

Reduce the single and cumulative doses of acetaminophen to which consumers are exposed, thus decreasing the potential for exceeding the toxic threshold of the drug that could cause liver injury.

Considerations Related to Incidence of Hepatotoxicity (liver injury)

- Since the currently recommended dose of 4 grams per day is considered safe for most people. this option is primarily intended to reduce unintentional overdose associated with misuse and duplicate dosing.
- Individuals who, for a variety of reasons (e.g., existing liver disease), are particularly susceptible to liver injury from acetaminophen may benefit from reduction in maximum recommended doses.
- Databases about liver injury cases associated with overdose generally do not provide sufficiently specific information about the doses taken to estimate the potential impact of this option. In one study, the median dose of acetaminophen ingested by 77 consumers with an unintentional overdose was 7.5 grams per day. 18 If it is presumed that these consumers took 1000 mg doses of formulations of acetaminophen that contained 500 mg per tablet or capsule, replicating intake of the same number of tablets or doses of acetaminophen, but with 325 mg of acetaminophen per tablet or capsule and 650 mg per dose, the median total dose for this group would be 4.875 grams, much closer to the current maximum recommended dose.
- OTC 500-mg, single-ingredient tablets and capsules make up 92% of U.S. sales of singleingredient acetaminophen. 19 If consumers feel that the maximum recommended dose of 650 mg is ineffective, they could respond by:
 - Increasing their consumption of lower strength product (e.g., to 975 mg per dose)
 - Switching to alternative treatments, such as NSAIDs, thus reducing incidence of overdose, but potentially increasing incidence of NSAIDs-related side effects.
- Rx combination products containing 500 mg or more of acetaminophen are common (e.g., 87% of units sold in the case of the hydrocodone/acetaminophen combination, 20 the most frequently dispensed acetaminophen-containing narcotic). There are currently insufficient data to support whether a change in acetaminophen dose in prescription combinations would substantially affect efficacy.

¹⁸ Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Lee WM et al. Acute Liver Failure Study Group (ALFSG). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology, 2005 Dec; 42(6):1364-72.

¹⁹ IMS Health, IMS National Sales Perspectives™, Year 2005, Extracted 4/09.

²⁰ Ibid.

Considerations Related to Implementation

- Although many OTC combination products already contain 325 mg of acetaminophen per dosage form, other products would need to be discontinued or require reformulation at a cost to manufacturers that would likely be passed on to consumers. FDA estimates that at least 143 Rx combination NDAs would have to be discontinued or reformulated.²¹
- FDA would have to determine whether efficacy trials would be required for reformulated, lower dosage NDA and ANDA combination products.

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²¹ Analysis of acetaminophen containing products in Orange Book. URL: http://www.fda.gov/cder/ob/. Accessed April 15, 2009.

Option 1b: Restrict currently recommended maximum adult daily dose, single adult dose, and dosage form strengths to Rx only status

Current Situation

All acetaminophen, single-ingredient products are sold OTC.

Option

The 325 mg per tablet or capsule would remain available OTC. Any formulation higher than that, such as 500 mg per tablet or capsule, would be available by prescription only. This option could be implemented in conjunction with option 6a, in which the recommended maximum OTC doses are reduced. With this option, products intended to deliver a maximum dose of 1000 mg (maximum daily dose 4 grams) would be made available Rx only.

Intended Effect

To allow higher doses of acetaminophen to remain available, but with a prescriber's oversight.

Considerations Related to Incidence of Hepatotoxicity (liver injury)

 Added prescriber oversight via the Rx route could facilitate reducing the risk of acetaminophen overdose.

Considerations Related to Implementation

- Medical office visits required to obtain a prescription may entail additional monetary costs to consumers, such as copayments and potential mark-up costs by pharmacies, and treatment delays.
- Manufacturers would have to develop, submit, and have FDA review NDAs or ANDAs for new Rx products. Manufacturers would also have to address associated promotion and supply issues.
- Among those OTC products that have NDA or ANDA applications, the only single-ingredient tablet is a 650-mg, extended release version of acetaminophen. Most other candidate products are either suppositories or combination products that contain other ingredients such as caffeine or pseudoephedrine.²² Interested sponsors would need to file new NDA or ANDA applications.

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²² Analysis of FDA's Orange Book (April 16, 2009).

Option 2: Establish package size limits for OTC products

Current Situation

Acetaminophen can be purchased OTC in large amounts, including bottles that contain hundreds of doses.

Options

More than one potential option exists under this general category.

- Limit the number of acetaminophen doses that can be contained in each package of OTC acetaminophen product
- Require acetaminophen tablets to be packaged in blister packs instead of bottles
- Impose restrictions on sales to limit the amount of acetaminophen that may be purchased by an individual at any one time.

Intended Effect

- To decrease the incidence of intentional ingestion of large overdoses by making it more difficult to accumulate large numbers of tablets.
- Blister packs could also help consumers track how many pills they have taken.

Considerations Related to Incidence of Hepatotoxicity (liver injury)

- Limits on amounts of OTC acetaminophen that could be purchased at one time could reduce incidence of overdose due to intentional injury.
- Limiting the availability of acetaminophen could move consumers to use other analgesics to treat pain with their attendant risk of adverse effects. ²³

Considerations Related to Implementation

• Limiting package size could cause substantial inconvenience to consumers, particularly to those who use OTC acetaminophen routinely under a doctor's care to treat chronic pain or arthritis.

- Blister packs could further adversely affect consumers (especially those with arthritis) because of the extra effort it takes to open blister packs.
- Manufacturer repackaging, whether in smaller container sizes, or blister packs could be costly and such costs could be passed on to consumers.

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²³ Data from the experience of mandatory package size restriction and voluntary sales restriction in the United Kingdom (U.K.) will be discussed at the upcoming advisory committee. It is not known how the U.K. experience would translate to the U.S. marketplace.

Option 3: Require unit-of-use packaging²⁴ for Rx products

Current Situation

Most combination Rx drug products containing acetaminophen are controlled substances (Schedule II), which pharmacies often purchase in bulk and then repackage and re-label for dispensing to patients. The labels on the dispensed containers and the medication information provided with these products vary from pharmacy to pharmacy. How warnings are presented and how acetaminophen is identified as the active ingredient can differ significantly.

Option

Require *unit-of-use packaging* for Rx acetaminophen products. Unit-of-use packaging would enable FDA to standardize the information dispensed to consumers, including warnings and the list of active ingredients (i.e. use the term *acetaminophen* rather than *APAP*). This information would appear on the package dispensed to the patient, in addition to the pharmacy prescription labeling.

Intended Effect

 Consumers would receive consistently presented FDA-approved information on the risks associated with acetaminophen with all Rx combination acetaminophen products.

Considerations Related to Incidence of Hepatotoxicity (liver injury)

- Unit-of-use packaging would have the added benefit of improving delivery of a Medication Guide (it can be attached to the bottle or packed inside a carton) and alerting consumers to the risk of liver injury related to acetaminophen.
- The effect of such information on health outcomes would depend on the extent to which consumers read, understand and act on it.

Considerations Related to Implementation

 Unit-of-use packaging could raise manufacturer packaging costs and costs to pharmacies of Rx acetaminophen containing products by lowering bulk discounts and decreasing shelf storage capacity. These costs would likely be passed on to consumers and healthcare payers.

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²⁴ *Unit of use packaging* means the product comes to the pharmacy packaged for sale without having to be repackaged. Many products come to pharmacies in bulk, enabling the pharmacist to repackage to suit individual patient needs.

Option 4: Expand product warning information on prescription (Rx) combination products and prominently list acetaminophen as a product ingredient

Current Situation

FDA has recently issued new regulations concerning labeling of over-the-counter (OTC) products containing acetaminophen. ²⁵ As a result, this option is limited to labeling for Rx acetaminophen combination products (i.e., narcotic–acetaminophen). These products do not contain a prominent warning about the risk of liver injury related to acetaminophen use, nor do they contain patient-directed information about this risk. In addition, when Rx combination products are dispensed by pharmacists, acetaminophen is sometimes identified by different names on the pharmacy's container (e.g., *APAP*).

Option

The following changes could potentially be made to Rx acetaminophen combination product labeling:

- Require a standard warning about liver injury as a Boxed Warning
- Require a Medication Guide for patients focusing on the risk of liver injury
- Require that pharmacy-dispensed containers of Rx acetaminophen-containing products identify acetaminophen using the full name, rather than APAP or another identifier

Intended Effect

- The Boxed Warning would give prescribers better information about the risks of acetaminophen overdose to raise awareness of acetaminophen-associated risks of liver injury.
- The Medication Guide and improved pharmacy labeling of containers could facilitate improved decision-making by prescribers and consumers to reduce the risk of acetaminophen overdose.

Considerations Related to Incidence of Hepatotoxicity (liver injury)

Unintentional overdoses make up approximately 54% of acetaminophen-related poison center calls.²⁶ Possible reasons may include: patients do not realize that their Rx pain medicines contain acetaminophen and patients do not know that they should not combine their Rx pain medicine with other Rx or OTC medicines that contain acetaminophen.

Considerations Related to Implementation

 Manufacturers would accrue additional costs that would likely be passed on to consumers and healthcare payers.

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²⁵ Organ-Specific Warnings; Internal Analgesic, Antipyretic, and Antirheumatic Drug Products for Over-the-Counter Human Use; Final Monograph (Docket No. FDA-1977-N-0013), 74 FR 19385 (April 29, 2009).

²⁶ 2005 Toxic Exposure Surveillance System data.

Option 5a: Eliminate OTC combination acetaminophen products

Current Situation

Many OTC products (hundreds) contain acetaminophen and other active ingredients. Consumers are not always aware when acetaminophen is present in the medicines they use.

Option

Eliminate OTC combination acetaminophen products.

Intended Effect

This could help prevent overdose resulting from unknowingly taking multiple OTC acetaminophen-containing medicines. The option would possibly also reduce the incidence of consumers combining OTC acetaminophen-containing products with Rx products containing acetaminophen, especially when the Rx acetaminophen product is not clearly labeled, or is labeled as *APAP*.

Considerations Related to Incidence of Hepatotoxicity (liver injury)

- Data from the 2005 Toxic Exposure Surveillance System suggest that among all poison center calls involving acetaminophen-containing products, 6.3% (3,845/61,289) of those requiring treatment could be attributed to overdosing on OTC combination products. In the study, 1.5% (41 of the 2,698 reported) involved major injury cases attributed to OTC combination products.
- Data from the 2005 Toxic Exposure Surveillance System show that 2.9% (3,423/116,613) of poison center calls involving acetaminophen-containing products involved intentional overdoses of OTC combination-products. The data do not specify whether the intent was suicidal or suicide gesture.

Considerations Related to Implementation

• Manufacturers will need to reformulate their existing products at some cost.

Option 5b: Eliminate combination Rx acetaminophen products

Current Situation

Many Rx products contain acetaminophen in combination with other active ingredients. Consumers are not always aware when acetaminophen is present in Rx combination products and may take both OTC and Rx medicines containing acetaminophen at the same time, possibly resulting in overdose.

Option

Eliminate combination Rx acetaminophen products.

Intended Effect

This option could help prevent overdose by reducing the number of Rx products containing acetaminophen.

Considerations Related to Incidence of Hepatotoxicity (liver injury)

- Data from the 2005 Toxic Exposure Surveillance System show that 54% (1,470/2,698) of poison center calls involving acetaminophen-containing products that resulted in major injury involved Rx combination-products. (It is not clear how many of these injuries resulted from overdose of acetaminophen versus the narcotic component of the combination product.)
- A 275-patient study of acetaminophen-induced acute liver failure found that 63% of unintentionally overdosed consumers, and 18% of intentionally overdosed consumers had taken acetaminophen-containing narcotic products prior to injury.²⁷
- In the absence of combination hydrocodone—acetaminophen products, Rx NSAIDs are an alternative therapy. However, it is likely that many consumers receiving hydrocodone—acetaminophen products have already failed or are intolerant of NSAIDs for pain management. Other patients, who are getting ready to have surgery or recently had surgery, may not be able to use an NSAID when the risk of bleeding is a concern. The NSAID GI risk alone ²⁸ results in greater overall morbidity and mortality than the risk of serious hepatotoxicity with acetaminophen. The other alternative therapies are single ingredient Schedule II opioids, such as oxycodone, morphine, hydromorphone and oxymorphone. However, these are often desirable targets for misuse and abuse because abusers know they can take multiples of these without worrying about exposure to acetaminophen. Also, as these are Schedule II products, patients are required to fill prescriptions monthly to comply with the restrictions imposed by the Controlled Substances Act, rather than being able to obtain a three-month supply with one visit to the pharmacy. This could represent a substantial burden for elderly patients and others with limited mobility as well as for patients who live at a distance from a pharmacy.

Considerations Related to Implementation

- Hydrocodone
 –acetaminophen combination products are the most frequently prescribed analgesic
 and the most frequently dispensed Rx drug product in the United States.
- There are currently no approved single-agent hydrocodone products available in the United States. More than 240 NDA/ANDA combination applications would be affected by this option.
- For development of hydrocodone single-agent formulations, implementation would include:

²⁷ Larson AM, Polson J, Fontana RJ, Davern TJ, Lalani E, Lee WM et al. Acute Liver Failure Study Group (ALFSG). Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology*, 2005 Dec: 42(6):1364-72.

²⁸ ACCF/ACG/AHA 2008 expert consensus document on reducing the gastrointestinal risks of antiplatelet therapy and NSAID use. Am J Gastroenterol, 2008 Nove; 103(11) 2890-907. Epub 2008 Oct 3.

- Submission of NDAs and ANDAs for single-ingredient hydrocodone products, which may also require clinical studies for demonstration of efficacy.
- Reformulation costs

Option 6: Limit dosing formulations for OTC liquid presentations

Current Situation

Liquid products, primarily for treating children, are available in different concentrations. Liquid acetaminophen formulations intended for use in infants are typically more concentrated than those for older children to enable dosing using less liquid. It is possible to mistakenly overdose an older child by giving him or her a product intended for an infant. In addition, regulations do not require that a measuring device be included in product packages.

Option

- Restrict OTC liquid acetaminophen suspensions to one concentration, either 160 mg per 5 mg concentration or develop a new concentration.
- Require manufacturers to include in each package a measuring spoon or container, properly calibrated and marked for correct product dosing.

Intended Effect

- Prevent overdoses caused by administering the wrong dose. This is of concern, particularly if parents mistakenly select the more concentrated infant formulation to administer to older children.
- Ensure availability of an accurate measuring device (spoon or container), thereby increasing the likelihood of a correct dose at the time acetaminophen is administered.

Considerations Related to Incidence of Hepatotoxicity (liver injury)

- This intervention targets the main cause of serious adverse events from acetaminophen use in children.
- A study of AERS reports from 1998 to mid-2001 found that 84% of the 25 acetaminophen-related liver injury events reported in pediatric patients were caused by medication errors. It remains unclear, however, how many of the cases were related to one or more of the following:
 - Use of an improper measuring device
 - Dosing the wrong concentration
 - Lack of dosing information for children under two years of age
- Eliminating the possibility of confusing two concentrations and providing a dosing device should help reduce all of these types of errors, resulting in a lower incidence of hepatotoxicity in pediatric patients.
- Infants may have trouble swallowing a large dose of a less-concentrated liquid formulation, which could result in underdosing.

Considerations Related to Implementation

- Prescribers and parents of infants will need guidance about changes in formulations.
- Manufacturers could incur reformulation costs, especially if the required concentration is not in production at this time.

Summary and Next Steps

The regulatory and public health challenges presented by acetaminophen-related liver injury are complex. From a public health standpoint, it must be considered that although the drug is both widely used and very effective—and does not lead to toxicity in the vast majority of individuals—when liver injury does occur it can be catastrophic, resulting in complete liver failure. There is clearly a high risk of acetaminophen-induced liver injury when a large overdose is ingested, such as in a suicidal attempt. Beyond this, little information exists to clarify: how possibly multiple components of the problem contribute to liver injury; the relative importance of a given individual's baseline risk for liver injury (e.g., genetic or metabolic factors); or the degree to which consumer knowledge and behaviors related to medicine use contribute to unintended overdose.

Over the past decade, FDA has initiated several activities to attempt to stem the public health burden of acetaminophen injury. However, more needs to be done. It is time to consider what additional measures the agency could take. The options outlined above have been carefully considered, and all have both benefits and costs. Whether the potential gain from implementing any or all of them could be expected to balance the burden is a matter that we hope our expert Advisors will discuss on June 29 and 30, 2009. For more Information about the meeting, including its location, background materials, and the agenda are available on the FDA Web site:

http://www.fda.gov/cder/audiences/acspage/meetings/joint_meeting_dsarm_ndac_aisdac_20090630.htm.



MEMORANDUM

Department Of Health and Human Services Food and Drugs Administration Center For Drug Evaluation and Research

Date: May 22, 2009

From: Charles Ganley, M.D., Director

Office of Nonprescription Products

Gerald Dal Pan, M.D, M.H.S., Director Office of Surveillance & Epidemiology

Bob Rappaport, M.D., Director

Division of Anesthesia, Analgesia, and Rheumatology Products

Subject: Background Package for June 29-30, 2009 Meeting

To: Advisory Committee Members

Drug Safety and Risk Management Committee, Anesthetic and Life

Support Drugs Advisory Committee and Nonprescription Drugs Advisory

Committee

Thank you for agreeing to serve at our upcoming joint advisory committee meeting on June 29-30, 2009. Attached you will find the background package for the meeting, the purpose of which is to discuss the public health problem of liver injury related to the use of acetaminophen in both over-the-counter (OTC) and prescription products. Over the past decade, FDA has taken a number of steps to mitigate the risk of liver injury related to this important drug. We are holding the meeting because we are interested in your input regarding the potential implementation of additional risk minimization strategies.

The background package has two components:

• A scientific review paper and recommendation statement from CDER's Acetaminophen Hepatotoxicity Working Group. This document was finalized February 26, 2008, for review by the Center Director. The group was tasked with reviewing recent findings from the published literature, focusing primarily on data published since a 2002 FDA advisory committee meeting about acetaminophen liver injury. The Working Group recommended that specific action steps be implemented by FDA to reduce the occurrence of acetaminophen hepatotoxicity. The actual report of the working group comprises approximately 32 pages and the remaining 231 pages includes supporting documents in an appendix. Some

outdated material has been redacted and updated information will be presented at the advisory committee meeting.

An Options Paper written by CDER staff to summarize the full scope of
interventions that FDA has considered, in order to facilitate your discussion.
This paper presents various topics considered by the Acetaminophen
Hepatotoxicity Working Group as options for further discussion. Following an
explanation of contributing factors and past FDA actions, each of six options is
identified with considerations about its implementation and potential impact on
reducing acetaminophen associated liver injury.

It is anticipated that a short addendum to this background package will be forwarded in the near future.

At the advisory committee meeting, we will present background information, as will the regulated industry, about the various regulatory processes that apply to products containing acetaminophen, the type and extent of products sold, and the bases of currently recommended acetaminophen doses in OTC and prescription products. Clinically important aspects of acetaminophen dosing and metabolism will be discussed. Information will be presented about the toxicity of acetaminophen, with focus on current epidemiologic profiles of liver injury databases and the complex role that consumer behavior plays in sustaining this public health problem.

Following the presentations, you will be asked to comment on your perception of the magnitude of the problem, the extent to which further intervention is warranted, and the type of interventions expected to be beneficial. Certain considerations will be further explained (e.g., the anticipated timeframe for implementation of each option), but many aspects of the potential impact of options (e.g., reduction in number of transplant cases) can not be precisely estimated. For some options, consideration will need to be given to the potential for shifting risks (e.g., from acetaminophen products to another drug class), rather than eliminating risks. Finally, you will be asked to assist the FDA in weighing the various knowns and unknowns to construct a rational risk minimization strategy.

We hope that these background materials are useful in your preparation for the meeting and look forward to your participation.